Acute Heroin Overdose

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Acute heroin overdose is a common daily experience in the urban and suburban United States and accounts for many preventable deaths. Heroin acts as a pro-drug that allows rapid and complete central nervous system absorption; this accounts for the drug's euphoric and toxic effects. The heroin overdose syndrome (sensitivity for diagnosing heroin overdose, 92%; specificity, 76%) consists of abnormal mental status, substantially decreased respiration, and miotic pupils. The response of naloxone does not improve the sensitivity of this diagnosis. Most overdoses occur at home in the company of others and are more common in the setting of other drugs. Heroin-related deaths are strongly associated with use of alcohol or other drugs. Patients with clinically significant respiratory compromise need treatment, which includes airway management and intravenous or subcutaneous naloxone. Hospital observation for several hours is necessary for recurrence of hypoventilation or other complications. About 3% to 7% of treated patients require hospital admission for pneumonia, noncardiogenic pulmonary edema, or other complications. Methadone maintenance is an effective preventive measure, and others strategies should be studied.

From the dark poppy a soporific is obtained by making incision in the stalk, when the buds are forming . . . it is not only a soporific, but if too large a dose be swallowed the sleep even ends in death.
 Pliny the Elder, 23–79 AD (1)

The United States is in the midst of another heroin epidemic. Heroin-related emergency department visits doubled from 33 900 in 1990 to 70 500 in 1996 (2). In 1993, heroin was implicated in more than 3805 deaths nationwide (3). Both urban and suburban emergency departments treat patients with heroin overdoses daily and hospitalize 3% to 7% of these patients for related complications (4, 5).

Heroin, also known as diacetylmorphine, was first synthesized by the Bayer Company in 1889 as a "less addicting morphine substitute" (6) (**Figure**). Heroin has become cheaper and more readily available in recent years, and a new generation of increasingly younger heroin users have new patterns of drug use (7). In persons who regularly inject heroin, the average annual mortality rate is 2%; half of this rate is attributable to overdose (8–13). This rate is 6 to 20 times the mortality rate expected in non–drug-using peers (14).

I review the clinically relevant pharmacology of heroin and naloxone, the epidemiology of fatal and nonfatal heroin overdose, the clinical diagnosis of heroin overdose, appropriate treatment, complications, and prevention strategies.

Methods

All relevant English-language articles identified through the MEDLINE database from 1988 through January 1998 were systematically searched by using the following key words: *heroin*, *poisoning*, *opiates*, and *naloxone*. Selected references from these articles and appropriate textbooks were also reviewed.

Pharmacology

Heroin produces its effects as an agonist on the mu, kappa, and delta receptors in the central nervous system. Mu_1 receptors are responsible for most of the analgesic effects, and Mu_2 receptors are responsible for respiratory depression, delayed gastrointestinal motility, miosis, euphoria, and physical dependence (15). Kappa agonists produce analgesia separately from mu receptor function and play a part in miosis, respiratory depression, and dysphoria. Delta receptors mediate spinal analgesia but are also found in cortical regions. Miosis is mediated by a mu receptor–related excitatory action at the parasympathetic nerve that innervates the pupil (16). Respiratory depression is caused by a direct effect on the brainstem respiratory centers that primarily occurs through a reduction in responsiveness to carbon dioxide.

Heroin is rapidly absorbed by all routes of administration. Intravenous heroin peaks in the serum in less than 1 minute (17), intranasal and intramuscular heroin peaks in 3 to 5 minutes (18), and subcutaneous heroin peaks in 5 to 10 minutes (19). Heroin is more lipid soluble than morphine and other opiates; thus, it crosses the blood–brain barrier within 15 to 20 seconds and achieves relatively high brain levels (19, 20). Sixty-eight percent of intravenous heroin is absorbed into the brain compared with less than 5% of intravenous morphine (21). This lipid solubility allows the rapid deposition

of heroin and its metabolites in the central nervous system and accounts for both the "rush" experienced by users and the toxicity.

Within 5 to 10 minutes, heroin in the central nervous system is hydrolyzed to monoacetylmorphine. Over 20 to 30 minutes, monoacetylmorphine is metabolized to morphine (22, 23). Heroin has agonist effects at the mu and delta receptors. Monoacetylmorphine has significant analgesic effects at the mu receptor and at the delta receptors in the brain and the spinal cord (24, 25). Peripheral tissues (blood, kidney, and liver) can also hydrolyze heroin to 6-monoacetylmorphine and then to morphine (17, 19, 20, 26).

Any circulating serum morphine is transformed into morphine-3-glucuronide or morphine-6-glucuronide by the liver and, to a lesser extent, the kidney (27). These water-soluble compounds are more readily excreted in urine or bile. Morphine-6-glucuronide has been demonstrated to have its own significant analgesic properties (28, 29).

The pharmacology of heroin explains why it is seven times more toxic than morphine and three times more toxic than monoacetylmorphine when given intravenously (19). The route of heroin administration also strongly affects the drug's potential to cause death or overdose. Most fatal and nonfatal heroin overdoses occur when the drug is administered intravenously. A small number of heroin-related deaths have been associated with intranasal administration (30–35). In one series (4), the intramuscular and subcutaneous routes accounted for only 0.3% and 0.5% of nonfatal heroin overdoses, respectively. These routes allow extensive peripheral hydrolysis and therefore limit toxicity (19). Only one death from oral heroin administration has been reported (36).

Naloxone is a potent antagonist at the mu, kappa, and delta receptors that is devoid of agonist activity (37, 38). It is readily absorbed intravenously (39), intramuscularly, and via endotracheal tube (40, 41). In its oral form, naloxone undergoes extensive hepatic metabolism and is inactive. Because of its high lipid solubility, it rapidly enters the central nervous system and has a rapid onset of action (39, 42). Peak brain levels of naloxone occur within 15 minutes and decline by 50% within the first hour. After intravenous injection, the effects of naloxone occur in 1 to 2 minutes and last 45 to 90 minutes. Naloxone is hepatically metabolized to naloxone-3-glucuronide, an inactive compound that is renally excreted.

Epidemiology

The extensive literature on heroin-related deaths was recently reviewed (14). Heroin-related deaths have many causes and occur in a heterogeneous group of patients. Most deaths occur among heroin users who are, on average, in their late twenties to early thirties (43, 44), have used heroin for 5 to 10 years (8), and have significant drug dependence (44). Most heroin-related deaths occur in the company of other people, and medical help is not sought or is sought too late (14, 44). Instant death from heroin injection does not seem to be the norm; most decedents are estimated to have died 1 to 3 hours after injection, a time interval that would allow intervention (44). Only a minority of heroin-related deaths (17%) occur among novice users (44).

In many heroin-related deaths, morphine levels alone do not account for the fatal outcome. The serum morphine levels detected in postmortem analysis have been skewed toward the lower end of the range of lethal and have commonly been found to be no higher than levels in heroin users who died of other causes (44–47). Serum morphine levels have also considerably overlapped between patients with heroin-related death and a control group of active heroin users who were alive (46). Similarly, brain morphine levels in patients who died of heroin-related causes have been inconsistent (48, 49).

Multiple drug use is common in heroin-related deaths. Most patients who die of heroin-related causes have significant alcohol (29% to 75%) or benzodiazepine (5% to 12%) levels (14, 34, 43–45, 47, 50–52). One study demonstrated that patients with high alcohol levels required much lower morphine levels to cause death (43). The combination of heroin with a respiratory depressant probably potentiates the chance of causing death. Concurrent intoxication may also make the heroin user more prone to risky behavior and dosing.
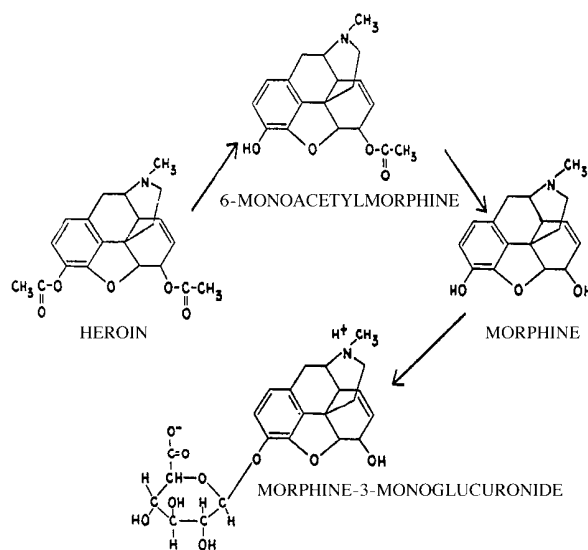

Figure. Metabolic pathway of heroin.

Table. Diagnosis and Treatment of Acute Heroin Overdose

Diagnosis
  Altered level of consciousness plus one of the following:
    Respiratory rate <12 breaths/min
    Miotic pupils
    Circumstantial evidence or history of heroin use
Treatment
  Assessment of ventilation and perfusion
    Patients with adequate ventilation
      Observation alone until normal level of consciousness
    Patients with inadequate ventilation
      Bag-valve-mask ventilation with 100% oxygen
      Naloxone, 0.2–0.4 mg, intravenously, subcutaneously, or
        intramuscularly
      Repeated dosing with naloxone, 2 mg, if no improvement in 5–7
        minutes
      Consideration of endotracheal intubation for the following reasons
        Inability to ventilate adequately with bag-valve-mask ventilation
        Poor oxygenation despite adequate ventilation
        Persistent hypoventilation after second dose of naloxone
  Patients with a complete naloxone response
    Observation for 2–3 hours for complications or resedation
    Repeated naloxone only for clinically significant hypoventilation
    Chest radiography for patients with pulmonary symptoms
    Appropriate substance abuse referral
  Patients with incomplete diagnosis
    Higher doses of naloxone for potential oral opiate intoxication
    Reconsideration of diagnosis

Several investigators have interviewed active heroin users about their experiences with nonfatal heroin overdose (53–56). These studies show that 23% to 33% of active heroin users had experienced a nonfatal heroin overdose in the past year (53, 56) and that 68% had ever had such an experience (55). Most active heroin users (86%) had witnessed an overdose, half of which had occurred in the previous year (54). Calling an ambulance was the first action in only 14% of cases; an ambulance was ultimately called for just more than half of these patients. The fear of police involvement was the major stated reason for not using the 911 emergency system.

One study (55) reported that 66% of nonfatal overdoses occurred in the home and that 85% occurred in the company of other people. Intravenous heroin use accounted for almost all overdoses (4, 56). Witnesses of a heroin overdose have estimated that the mortality rate of such overdoses is 5% (54). Only a minority of overdoses occurred in the first year of heroin use, and there was no indication of over-representation of overdoses occurring on weekends (55). A consistent number of patients (13%) reported their last overdose after release from incarceration (55, 57).

Several reasons were given for the nonfatal overdose: higher than usual dose (55%), stronger than usual heroin (40%), heroin combined with ethanol (30%), use of heroin after abstinence (28%), and deliberate self-harm (4%) (53, 56). A drug user who experiences a nonfatal heroin overdose is more likely to have had a longer history of drug use, more likely to be more dependent on heroin, and unlikely to be receiving addiction treatment (55). As was

seen with heroin-related deaths (46), the simultaneous use of other drugs is a major risk factor for overdose. More than 70% of drug users reported using another drug at the time of their last overdose (55). Serum drug testing in patients who had overdosed showed that almost all of these patients had combined heroin use with alcohol or benzodiazepine use (58).

Diagnosis

The opiate intoxication syndrome was first described in the 1970s as a triad of depressed level of consciousness, miotic pupils, and decreased respiration (**Table**) (59, 60). Since then, many authors have used a response to naloxone as confirmation of heroin intoxication. Unfortunately, no well-designed studies using quantitative serum drug levels have assessed the sensitivity and specificity of these clinical criteria for diagnosing a heroin overdose.

One study (61) examined persons with heroin overdose who presented to an emergency department and were classified as being in "a state of coma due to heroin self-administration followed by full recovery after treatment with naloxone." However, this study did not state the specific criteria used to make this diagnosis (61). In this study, serum samples were drawn before naloxone administration. All 54 patients had clinically significant serum levels of morphine and morphine-6-glucuronide, and these combined levels correlated well with the patient's Glasgow Coma Scale score on arrival at the emergency department. This study was not designed to examine the sensitivity and specificity of a clinical response to naloxone.

Another series of patients with presumed heroin overdose who responded to naloxone underwent extensive serum quantitative drug testing (58). The clinical variables used to diagnose heroin overdose in this study were not well defined. Of the 53 patients, 45 had clinically significant serum drug levels that were consistent with heroin intoxication, 6 had detectable levels of other opiates, and 2 had no detectable levels of serum opiates.

Hoffman and colleagues examined the usefulness of clinical criteria to predict a final diagnosis of opiate overdose (62). These clinical criteria include a Glasgow Coma Scale score of 12 or less combined with one of the following: respirations of 12 breaths/min or less, miotic pupils, or circumstantial evidence of drug use. All study participants were patients treated by paramedics for abnormal mental status of any cause in a portion of Los Angeles County, California, for 1 year. All of these patients received a 2-mg parenteral dose of naloxone and were categorized into three groups of naloxone response: complete responders, partial responders, and nonre-

sponders. Of the 730 patients studied, 3.4% were complete responders, 4.4% were partial responders, and 92% were nonresponders.

A clinical diagnosis of opiate intoxication was made by a blinded reviewer; no toxicologic analyses were done for these patients. The authors determined that 25 of the 730 patients with an abnormal mental status had clinical opiate overdose. The use of clinical criteria alone had a sensitivity of 92% and specificity of 76% for diagnosing opiate overdose. The addition of a complete naloxone response to the clinical criteria had a sensitivity of 86% and a specificity of 97%. Partial responses to naloxone were unreliable for diagnosing opiate intoxication; this condition was ultimately diagnosed in only 2 of the 32 partial responders.

The major conclusion of Hoffman and colleagues' study was that most patients with undifferentiated abnormal mental status and no clinical signs of opiate intoxication would not benefit from naloxone and that no occult opiate intoxications would be missed if this drug was not given. No similar studies have been done, but current clinical practice refrains from indiscriminate naloxone use in these patients (63).

Several indirect conclusions about the treatment of heroin overdose can be reached from Hoffman and colleagues' study. The authors concluded that clinical variables are reasonably beneficial for diagnosing acute heroin intoxication. The addition of naloxone only worsened the sensitivity for making this diagnosis. The utility of naloxone as a diagnostic aid is questionable; the drug should be used only to treat life-threatening respiratory depression. Another important point is that not every patient who responds to naloxone has an opiate overdose. Of the 25 complete naloxone responders, 19 were determined to have true opiate overdoses; 6 had false-positive responses and ultimately received a diagnosis of seizure or a closed head injury.

It is also unclear whether every patient with a heroin overdose will respond to naloxone. Four patients with a clinical opiate overdose who were not identified by the clinical findings did not respond to naloxone; they constitute the only false-negative naloxone responses reported in the literature. Unfortunately, Hoffman and colleagues did not discuss the clinical details of these patients.

Treatment

The treatment of a patient presenting with acute heroin overdose begins with assessment of the adequacy of ventilation (**Table**). If the patient is breathing well without support, naloxone should not be administered and observation alone should suffice. Most patients, however, have inadequate respiration and should receive bag-valve-mask ventilation fol-

lowed by parenteral naloxone therapy. Endotracheal intubation should be avoided unless the patient does not respond to naloxone within 5 to 10 minutes of administration or there is some other compelling reason for invasive airway management.

The proper naloxone dose and route of administration are matters of debate. In a hypoventilating patient suspected of having heroin intoxication, an initial parenteral dose of 0.4 mg of naloxone, followed by a higher dose (1 to 2 mg) if no response occurs in 3 to 5 minutes, is generally recommended. Lower starting doses can be used for obvious heroin overdoses as long as ventilatory support is adequate (63). Higher naloxone doses may be necessary to reverse the effects of semisynthetic oral opiates (64).

Intravenous administration has been the preferred route for naloxone, but both the intramuscular and subcutaneous routes have also been shown to be effective (4, 65). A recent prehospital study (65) reported that intravenous (0.4 mg) and subcutaneous (0.8 mg) naloxone administration yielded similar results (65). The mean interval to adequate ventilation (10 breaths/min) was 9.3 minutes for the intravenous naloxone group and 9.6 minutes for the subcutaneous naloxone group. The rapid onset of intravenous naloxone was offset by the time required to place the intravenous line. No prospective clinical trials have compared intramuscular with intravenous administration of naloxone or examined different doses of the drug (66).

A patient with successfully treated heroin overdose and adequate ventilation should be observed in the emergency department for 2 to 3 hours. Naloxone is expected to lose efficacy in 20 to 40 minutes, and many patients will again develop signs of heroin intoxication (67). Further naloxone is indicated only for the few patients with recurrent significant respiratory compromise. Patients who have clinically significant cough or poor oxygenation should be evaluated with chest radiography.

Naloxone treatment of heroin overdose is associated with a small but consistent rate of such complications as seizures (68–70), arrhythmias (71, 72), and severe agitation (4, 73, 74). A prospective study of the clinical adverse effects of in-hospital naloxone therapy in clinically apparent heroin intoxication revealed that 1.6% of patients developed severe complications (75). These patients were given a mean intravenous naloxone dose of 0.2 mg, and all complications occurred within 10 minutes. Six of 453 patients given naloxone for heroin overdose developed complications: asystole in 1 patient, seizures in 3 patients, pulmonary edema in 1 patient, and violent behavior in 1 patient. Of note, the complication rate seen with naloxone therapy seems to be similar to or greater than that seen with flumazenil, an agent that many clinicians use with much trepidation.

Nalmefene, a long-acting specific narcotic antagonist, has been proposed as a substitute for naloxone (76, 77). When nalmefene was compared with naloxone in a prehospital, double-blind, randomized trial of clinical heroin overdose, naloxone more quickly improved spontaneous ventilation (78). In addition, one case report found that the prolonged withdrawal that predictably occurs with nalmefene was dangerous; as a result, this drug has limited usefulness for heroin overdose (79).

Complications

The hospitalization rate among patients with treated heroin overdoses has ranged from 3% to 7%, and the admission diagnosis has included noncardiogenic pulmonary edema (1% to 2.4% of patients), pneumonia (0.5%), possible endocarditis (0.25%), and a persistent altered mental status or respiratory depression (0.7% to 4%) (4, 5).

Noncardiogenic pulmonary edema is a complication of heroin overdose that has occurred less frequently in recent years. This complication, whose exact mechanism is unknown, has been associated with both heroin and naloxone (80–82). It is usually clinically apparent immediately or within 2 hours of administration of the drug and is manifested by rales, pink frothy sputum, significant hypoxia, and bilateral fluffy infiltrates on chest radiography. Most patients require mechanical ventilation because of severe hypoxia and respond in 24 to 36 hours with supportive care. This syndrome has been characterized as noncardiogenic on the basis of hemodynamic (83) and pulmonary fluid (84) analyses.

Earlier retrospective case series of patients hospitalized because of heroin overdose reported a rate of noncardiogenic pulmonary edema of 48% to 80% (30, 31, 59, 85). These studies did not provide the full denominator, which would have included hospitalized and discharged patients with heroin overdose. More recent case series of patients presenting with heroin overdose reported a rate of noncardiogenic pulmonary edema of 0.8% to 2.4% (4, 5, 86). These series are limited because of the short observation periods and limited follow-up (87).

This early experience is probably the reason for the extended observation period of 12 to 24 hours that is commonly quoted in many textbooks (64, 88). The optimal observation period for the development of noncardiogenic pulmonary edema in a patient with heroin overdose is likely to be several hours. Sixty-one of the 64 patients with noncardiogenic pulmonary edema reported in the literature had significant symptoms at arrival in the emergency department or within 2 hours of arrival (30–32, 85, 89–97). Only 3 patients have had delayed symptom onset while under medical observation (31, 98, 99).

The optimal observation period for patients with an acute heroin overdose would guarantee that most or all cases of noncardiogenic pulmonary edema would occur during medical observation. If we assume that the rate of this condition is twice the rate reported in recent series (5%) and extrapolate from published reports, 95% of cases would occur within the first hour of observation. A patient with a heroin overdose has a 4.75% chance of developing noncardiogenic pulmonary edema during a 2-hour observation period and a 0.25% chance of developing late-appearing symptoms. It seems unnecessary to commit hundreds of patients to 12- or 24-hour observation for such a small risk. Longer observation periods may be necessary for patients with methadone or other oral opiate overdoses.

Other complications related to injection drug use include rhabdomyolysis, the compartment syndrome, endocarditis, and wound botulism (100–107).

Prevention

The principles of harm reduction have been effectively applied to this difficult group of patients through needle-exchange programs initiated to reduce HIV infection (108). It is logical to predict that a multifaceted approach to reducing the harm caused by heroin overdose could be similarly effective (109).

Methadone maintenance has been shown to help protect against death from heroin overdose and other causes. One study comparing two groups of opiate addicts—one that received methadone maintenance and one that received no treatment—showed a large reduction in overdose-related deaths in the methadone group (110). Expanding current methadone maintenance treatment would probably have a notable effect on heroin-related deaths.

Simultaneous use of other drugs, such as alcohol or benzodiazepines, has long been implicated in heroin-related deaths (14, 43, 51, 92) and nonfatal heroin overdoses (54–56, 111). Certain periods in an opiate addict's life may be more dangerous than others. For example, the first 12 months after discontinuation of addiction treatment (8) and the first 2 weeks after release from incarceration (57) are periods in which the patient is at high risk for heroin overdose and death. Education about these issues, as well as encouragement of use of the 911 emergency system, may help reduce heroin overdoses.

The concept of "take home" naloxone as a method of preventing heroin overdose–related deaths has recently been discussed (109). One letter to the editor estimated that this treatment could save the lives of thousands of people each year in the United Kingdom alone (112). Most heroin users have substantial experience with parenteral administration

(113, 114), but self-injectable cartridges of naloxone or intranasal naloxone could make administration simpler and more effective.

These proposals raise several ethical issues and practical complications. In one study, approximately 80% of persons present during a companion's overdose were intoxicated themselves (54). The availability of naloxone may remove the deterrent effect of heroin dosing and could inadvertently increase the number of overdoses. Addicts' extreme distaste for the withdrawal caused by naloxone may make them reluctant to use it even if it is available. Patients may be unwilling to go to a hospital for observation after successful resuscitation at home; thus, patients with pulmonary and other complications will not receive timely medical care. The occasional seizure and other complications of naloxone use will occur in a less controlled environment. Despite these misgivings, the potential opportunity to prevent thousands of heroin-related deaths warrants the dispassionate exploration of this option.

Conclusion

Acute heroin overdoses are increasing across the United States and account for many preventable deaths. Heroin acts as a pro-drug that allows rapid central nervous system absorption; this accounts for the drug's euphoric and toxic effects. The physical examination findings of a patient with heroin overdose include an altered level of consciousness, substantially decreased respirations, and miotic pupils. Patients with significant respiratory compromise need treatment, such as airway management and parenteral naloxone. In patients with heroin overdose, naloxone is associated with a 1.6% rate of serious complications, including seizures and arrhythmias. Hospital observation for 2 to 3 hours is necessary for recurrent hypoventilation or other complications. One percent to 3% of patients with heroin overdose develop noncardiogenic pulmonary edema, and 0.5% to 1.0% develop pneumonia.

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